29. Sanders RD, Myles PR, Hubbard R, et al. Benzodiazepines increase mortality from pneumonia: Role of GABAergic signalling. *Anesthesiology*. 2011;A765.
30. Pandharipande PP, Sanders RD, Girard TD, et al; MENDS investigators. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. *Crit Care*. 2010;14(2):R38.
31. Vasilevskis EE, Pandharipande PP, Girard TD, Ely EW. A screening, prevention, and restoration model for saving the injured brain in intensive care unit survivors. *Crit Care Med*. 2010;38(suppl 10):S683-S691.
32. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med*. 1996;335(25):1864-1869.
33. Skrobik Y. Delirium prevention and treatment. *Anesthesiol Clin*. 2011;29(4):721-727.
34. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373(9678):1874-1882.

Counterpoint: Should Benzodiazepines Be Avoided in Mechanically Ventilated Patients? No

The preoccupation that critically ill patients should be free from pain, agitation, and anxiety while in intensive care motivates physicians to prescribe analgesics and sedatives. Benzodiazepines are part of what is meant to be pharmacologic optimization of patient comfort. How much sedation should be used, and for how long, has recently become the focus of scientific debate. At the heart of this deliberation is the conviction by many caregivers that sedation mitigates how traumatic the patient perceives the ICU experience to be. This notion is slowly being contradicted by data from follow-up studies.[1] In contrast, there is an emerging understanding that excessive sedation, with its short- or medium-term decreases in consciousness, is common and is associated with increased morbidity, mortality, and expenditure.[2,3] It is important to differentiate outcomes associated with excess sedation, which is harmful, from benzodiazepine use, which is not.

No benzodiazepine has all the ideal characteristics one would wish for in a sedative, such as rapid onset, rapid recovery, a predictable dose response, a lack of drug accumulation, and an absence of toxicity. But all benzodiazepines do share one desirable characteristic: They are inexpensive. The pharmacokinetic, pharmacodynamic, and pharmacogenetic effects inherent to this drug class are helpful in understanding their administration, and to the physician's interpretation of the data available in current sedation studies.

The γ-aminobutyric acid A cerebral neuronal receptor activation inherent to benzodiazepine activity is part and parcel of its anxiolytic, amnesic, sedating, hypnotic, and anticonvulsant effects.[4] Sensitivity to benzodiazepine effect increases with age, and benzodiazepine clearance decreases in the elderly.[5] Respiratory depression and systemic hypotension can occur when benzodiazepines are administered with other drugs, especially opioids, in patients with cardiovascular instability or respiratory failure, but these side effects compare favorably with those associated with other sedatives. All benzodiazepines are metabolized by the liver. Benzodiazepine clearance is reduced in patients with hepatic dysfunction.[6] Delayed emergence from sedation with benzodiazepines when benzodiazepines are administered continuously can be associated with advanced age, hepatic dysfunction, or renal insufficiency.[7]

The choice of benzodiazepine plays a role in determining its effects on individual patients, particularly when it comes to decreasing intermittent or continuous doses, or increasing administration intervals. The effect and elimination time of lorazepam are increased in patients with renal failure.[8] The active metabolites of midazolam and diazepam accumulate with prolonged administration, an effect heightened by renal dysfunction.[9] Diazepam saturates peripheral tissues, and its active metabolites can accumulate in patients with renal insufficiency, lengthening clinical effect duration.[10] Comparative studies of prolonged use of midazolam and lorazepam in patients in the ICU suggest greater variability and longer time to awakening with midazolam than with lorazepam.[11,12]

The response to acute physiologic stress, aggressive hemodynamic resuscitation, and organ dysfunction also alter drug response in the critically ill and in a critically ill individual over time. One example of this effect is the wide variations in serum albumin attributable to alterations in liver synthesis and dilution. This may affect highly protein-bound drugs, such as midazolam. The effects of acute illness and protein shifts on midazolam bioavailability may, thus, vary with fluid resuscitation and with variability in protein synthesis by the liver. The pharmacokinetics of midazolam were thought to be well characterized, with predictable pharmacodynamics in healthy adults. However, a recent study describing midazolam drug levels, half-life, and terminal half-life in nine critically ill patients with sepsis suggested considerable variability within a much broader range than had been reported in the literature to date, and in comparison with normal subjects,[13] with significant intra- and intersubject variability. In addition, terminal half-life, which is determined after drug infusion cessation, was prolonged in all nine patients with sepsis

Downloaded From: http://journal.publications.chestnet.org/ on 08/11/2012

and contrasted with previously published values in less ill populations. These characteristics are in keeping with the description of a pediatric critical care population in which lower midazolam elimination was observed in comparison with other studies in pediatric patients,[14] and these were felt to be attributable to such covariates as renal failure, hepatic failure, and concomitant administration of cytochrome P (CYP) 3A inhibitors, among others.

Medications that inhibit either CYP450 enzyme systems and/or glucuronide conjugation in the liver affect the clinical effect of benzodiazepines. The CYP450 3A4/5 pathway is shared by more than one-half of the medications administered in an ICU. Fentanyl and midazolam, for instance, are commonly coadministered in critical care and are extensively metabolized by the same CYP450 isoenzymes, namely, CYP3A4/5.[15] Further, genetic polymorphisms are associated with the functional level of expression of these enzymes (especially CYP3A5),[16] which may also predispose patients to highly variable CNS effects of midazolam. Excessive sedation can occur during coadministration of these drugs because of competitive inhibition and increased serum or tissue drug levels. Coadministration of fentanyl and midazolam,[17] of midazolam and voriconazole,[18] and of midazolam and fluconazole,[19] predictably increase midazolam blood levels and midazolam clinical effect.

Benzodiazepine-based continuous sedation has been associated with prolonged dependence on mechanical ventilation and increased ICU length of stay[20,21] in some studies but not in others.[22,23] No study accounted for patient age; renal or hepatic dysfunction; or other pharmacokinetic, pharmacogenetic, or drug-drug interactions to better illuminate whether these differences may have accounted for the discordant findings. More recent sedation trials describe study entry and study duration sedation levels; additional data on sedation assessments after benzodiazepines and other drugs have been discontinued would also illuminate the relevant variables, because of the half-life and metabolite variables mentioned earlier. Large differences in sedation practice have been highlighted with these sedation trial publications of baseline data; some trials,[24] such as the Awakening and Breathing controlled trial, entered patients whose average sedation level (measured by the Richmond Agitation and Sedation Scale [RASS]) suggested they were only responsive to pain (RASS levels of -4), whereas other sedation and analgesia titration trials described patients sedated quite lightly at baseline[25] (RASS levels of -0.4). Considering these elements at study entry and over time is important when reviewing publications; the risk or benefit of a given intervention may be associated with choice of molecule or level of sedation, and both variables should be available to the reader. If one of the molecules is a benzodiazepine, factors influencing its effect and duration should also be reported.

Several publications suggest an association between the dose of continuously administered benzodiazepine and delirium in patients who are critically ill.[26,27] Because continuously sedating patients with midazolam appears associated with a higher incidence of delirium than sedating patients with dexmedetomidine,[28] and because this difference is not seen when morphine is compared with dexmedetomidine,[29] midazolam has been presumed to be linked to delirium occurrence. The confusion assessment method-ICU screening tool was the tool used to detect ICU delirium in the studies describing less delirium with dexmedetomidine, a molecule that is associated with greater wakefulness than midazolam. Some authors have suggested that the confusion assessment method-ICU scoring may be affected by sedation[30]; the potential that the greater sedation seen and expected with midazolam was a confounder for delirium remains to be clarified before convincing conclusions can be drawn. The therapeutic effect of dexmedetomidine in delirium, currently under study, remains to be proven.

The importance of avoiding excessive sedation has been emphasized in recent years in publications suggesting that daily interruption of sedative infusions, titration of sedative dose and opiates to symptoms,[26] and minimization of drug administration are associated with patient benefits and reduced costs[31] and do not lead to accidental device removal or psychologic stress. No study has convincingly made the point that the type of drug makes a difference, with the caveat that studies to date have been limited to in-hospital events and were not long-term comparisons between drug classes and doses. Benzodiazepines are inexpensive, safe, and familiar to physicians and are readily adjusted to patient symptoms. Titrating, in particular adjusting and reducing sedative doses, as needed, to achieve the desired effect, is beneficial. Rigorous avoidance of iatrogenic (sedative-induced and inadvertent) coma is key; it reduces costs, the duration of mechanical ventilation, and the incidence of subsyndromal delirium,[26] a state between cognitive normalcy and full-blown delirium[32] detectable with the intensive care delirium screening checklist tool. Benzodiazepines can be adjusted in this manner and remain the most affordable sedative, both relevant determinants in our choices in pharmaceuticals.[33] The benefit of more expensive alternatives has yet to be shown in sedating (lightly and only as needed) the general critical care population.

Yoanna Skrobik, MD
Montreal, QC, Canada

DownloadedFrom:http://journal.publications.chestnet.org/on08/11/2012

Affiliations: From Soins Intensifs, Maisonneuve Rosemont Hospital, Universite de Montreal.
Financial/nonfinancial disclosures: The author has reported to *CHEST* the following conflicts of interest: Dr Skrobik is the lead physician in an investigator-initiated research project funded by Hospira; she receives no honoraria or income from that project as all funding serves to fund data collection.
Correspondence to: Yoanna Skrobik, MD, Hopital Maisonneuve Rosemont 5415 boul. de l'Assomption, Montreal, QC, H1T 2M4, Canada; e-mail: yoanna.skrobik@umontreal.ca
© 2012 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.
DOI: 10.1378/chest.12-1191

References

1. Treggiari MM, Romand JA, Yanez ND, et al. Randomized trial of light versus deep sedation on mental health after critical illness. *Crit Care Med*. 2009;37(9):2527-2534.
2. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med*. 2007;33(1):66-73.
3. Herridge MS, Tansey CM, Matté A, et al; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14): 1293-1304.
4. Greenblatt DJ, Harmatz JS, Shader RI. Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly. Therapeutic considerations (part I). *Clin Pharmacokinet*. 1991;21(3): 165-177.
5. Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA, Shader RI. Effect of age, gender, and obesity on midazolam kinetics. *Anesthesiology*. 1984;61(1):27-35.
6. Swart EL, Zuideveld KP, de Jongh J, Danhof M, Thijs LG, Strack van Schijndel RM. Population pharmacodynamic modelling of lorazepam- and midazolam-induced sedation upon long-term continuous infusion in critically ill patients. *Eur J Clin Pharmacol*. 2006;62(3):185-194.
7. Oldenhof H, de Jong M, Steenhoek A, Janknegt R. Clinical pharmacokinetics of midazolam in intensive care patients, a wide interpatient variability? *Clin Pharmacol Ther*. 1988; 43(3):263-269.
8. Greenblatt DJ, Ehrenberg BL, Gunderman J, et al. Kinetic and dynamic study of intravenous lorazepam: comparison with intravenous diazepam. *J Pharmacol Exp Ther*. 1989; 250(1):134-140.
9. Bauer TM, Ritz R, Haberthür C, et al. Prolonged sedation due to accumulation of conjugated metabolites of midazolam. *Lancet*. 1995;346(8968):145-147.
10. Ariano RE, Kassum DA, Aronson KJ. Comparison of sedative recovery time after midazolam versus diazepam administration. *Crit Care Med*. 1994;22(9):1492-1496.
11. Swart EL, Zuideveld KP, de Jongh J, Danhof M, Thijs LG, Strack van Schijndel RM. Comparative population pharmacokinetics of lorazepam and midazolam during long-term continuous infusion in critically ill patients. *Br J Clin Pharmacol*. 2004;57(2):135-145.
12. Pohlman AS, Simpson KP, Hall JB. Continuous intravenous infusions of lorazepam versus midazolam for sedation during mechanical ventilatory support: a prospective, randomized study. *Crit Care Med*. 1994;22(8):1241-1247.
13. Ovakim D, Bosma KJ, Young GB, et al. Effect of critical illness on the pharmacokinetics and dose-response relationship of midazolam. *Crit Care*. 2012;16(suppl 1):P330.
14. de Wildt SN, de Hoog M, Vinks AA, van der Giesen E, van den Anker JN. Population pharmacokinetics and metabolism of midazolam in pediatric intensive care patients. *Crit Care Med*. 2003;31(7):1952-1958.
15. Gorski JC, Hall SD, Jones DR, VandenBranden M, Wrighton SA. Regioselective biotransformation of midazolam by members of the human cytochrome P450 3A (CYP3A) subfamily. *Biochem Pharmacol*. 1994;47(9):1643-1653.
16. Fukasawa T, Suzuki A, Otani K. Effects of genetic polymorphism of cytochrome P450 enzymes on the pharmacokinetics of benzodiazepines. *J Clin Pharm Ther*. 2007;32(4): 333-341.
17. Oda Y, Mizutani K, Hase I, Nakamoto T, Hamaoka N, Asada A. Fentanyl inhibits metabolism of midazolam: competitive inhibition of CYP3A4 in vitro. *Br J Anaesth*. 1999;82(6): 900-903.
18. Saari TI, Laine K, Leino K, Valtonen M, Neuvonen PJ, Olkkola KT. Effect of voriconazole on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Clin Pharmacol Ther*. 2006;79(4):362-370.
19. Ahonen J, Olkkola KT, Takala A, Neuvonen PJ. Interaction between fluconazole and midazolam in intensive care patients. *Acta Anaesthesiol Scand*. 1999;43(5):509-514.
20. Cox CE, Reed SD, Govert JA, et al. Economic evaluation of propofol and lorazepam for critically ill patients undergoing mechanical ventilation. *Crit Care Med*. 2008;36(3):706-714.
21. Fong JJ, Kanji S, Dasta JF, Garpestad E, Devlin JW. Propofol associated with a shorter duration of mechanical ventilation than scheduled intermittent lorazepam: a database analysis using Project IMPACT. *Ann Pharmacother*. 2007;41(12): 1986-1991.
22. Hall RI, Sandham D, Cardinal P, et al; Study Investigators. Propofol vs midazolam for ICU sedation: a Canadian multicenter randomized trial. *Chest*. 2001;119(4):1151-1159.
23. Huey-Ling L, Chun-Che S, Jen-Jen T, Shau-Ting L, Hsing-I C. Comparison of the effect of protocol-directed sedation with propofol vs. midazolam by nurses in intensive care: efficacy, haemodynamic stability and patient satisfaction. *J Clin Nurs*. 2008;17(11):1510-1517.
24. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134.
25. Skrobik Y, Ahern S, Leblanc M, Marquis F, Awissi DK, Kavanagh BP. Protocolized intensive care unit management of analgesia, sedation, and delirium improves analgesia and subsyndromal delirium rates. *Anesth Analg*. 2010;111(2):451-463.
26. Pisani MA, Murphy TE, Araujo KL, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit Care Med*. 2009;37(1):177-183.
27. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104(1):21-26.
28. Riker RR, Shehabi Y, Bokesch PM, et al; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301(5):489-499.
29. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). *Anesthesiology*. 2009;111(5):1075-1084.
30. Kress JP. The complex interplay between delirium, sepsis and sedation. *Crit Care*. 2010;14(3):164.
31. Awissi DK, Bégin C, Moisan J, Lachaine J, Skrobik Y. I-SAVE study: impact of sedation, analgesia, and delirium protocols evaluated in the intensive care unit: an economic evaluation. *Ann Pharmacother*. 2012;46(1):21-28.

DownloadedFrom:http://journal.publications.chestnet.org/on08/11/2012

32. Ouimet S, Riker R, Bergeron N, Cossette M, Kavanagh B, Skrobik Y. Subsyndromal delirium in the ICU: evidence for a disease spectrum. *Intensive Care Med*. 2007;33(6):1007-1013.
33. Wunsch H. Weighing the costs and benefits of a sedative. *JAMA*. 2012;307(11):1195-1197.

Rebuttal From Dr Ely et al

Dr Skrobik's[1] counterpoint editorial does an excellent job of describing many of the characteristics that make benzodiazepines such a poor choice for sedation in the ICU, including delayed clearance and prolonged awakening, especially in patients with kidney injury, liver dysfunction, or advanced age (all common among patients in the ICU); tremendous variability in response; and alterations in metabolism when coadministered with many medications used in the ICU. We agree with her that benzodiazepines lack the characteristics of an ideal ICU sedative.

As we respond to the matters in dispute, we are reminded of our initial reluctance to write an editorial against the use of benzodiazepines for sedation in the ICU. We had reservations about being a "bully" against such a commonly used class of sedatives or against well-intentioned ICU practitioners. But Dr Skrobik's claim that "no study has convincingly made the point that the type of drug makes a difference

Table 1—*Randomized Trials Comparing Benzodiazepines With Alternative Sedatives in the ICU*

Study/Year	Population	Outcome(s) Improved
Benzodiazepines vs propofol		
Trials finding better outcomes with propofol		
Grounds et al[2]/1987	Cardiac surgery	Faster awakening
Aitkenhead et al[3]/1989	General ICU	More consistent awakening, faster weaning
McMurray et al[4]/1990	Cardiac surgery	Faster awakening
Carrasco et al[5]/1993	General ICU	More accurate sedation, faster awakening, lower costs
Roekaerts et al[6]/1993	Cardiac surgery	Faster awakening, earlier extubation
Ronan et al[7]/1995	Surgical ICU	Faster awakening
Sherry et al[8]/1996	Cardiac surgery	Lower costs
Chamorro et al[9]/1996	General ICU	Better ventilator synchrony, faster awakening
Barrientos-Vega et al[10]/1997	General ICU	Earlier extubation
Weinbroum et al[11]/1997	General ICU	Faster awakening
Sanchez-Izquierdo-Riera et al[12]/1998	Trauma ICU	Faster awakening
McCollam et al[13]/1999	Trauma ICU	Less oversedation
Hall et al[14]/2001	Mixed ICU	More accurate sedation, earlier extubation
Carson et al[15]/2006	Medical ICU	Fewer ventilator days
Trials finding no differences in outcomes		
Searle et al[16]/1997	Cardiac surgery	None
Kress et al[17]/2000	Medical ICU	None
Huey-Ling et al[18]/2008	Cardiac surgery	None
Trials finding better outcomes with the benzodiazepine		
None	…	…
Benzodiazepines vs remifentanil		
Trials finding better outcomes with remifentanil		
Breen et al[19]/2005	Mixed ICU	Shorter duration of mechanical ventilation
Muellejans et al[20]/2006	Cardiac surgery	Earlier extubation and ICU discharge
Rozendaal et al[21]/2009	Mixed ICU	Lighter sedation, shorter weaning time
Trials finding no differences in outcomes		
None	…	…
Trials finding better outcomes with the benzodiazepine		
None	…	…
Benzodiazepines vs dexmedetomidine		
Trials finding better outcomes with dexmedetomidine		
Pandharipande et al[22]/2007	Mixed ICU	More accurate sedation, more delirium/coma-free days
Riker et al[23]/2009	Mixed ICU	Lower prevalence of delirium, earlier extubation
Ruokonen et al[24]/2009	Mixed ICU	Shorter duration of mechanical ventilation[a]
Maldonado et al[25]/2009	Cardiac surgery	Lower incidence and duration of delirium
Esmaoglu et al[26]/2009	Eclampsia	Shorter ICU length of stay
Dasta et al[27]/2010	Mixed ICU	Lower ICU costs
Jakob et al[28]/2012	General ICU	Lighter sedation, fewer ventilation days
Trials finding no differences in outcomes		
None	…	…
Trials finding better outcomes with the benzodiazepine		
None	…	…

[a] According to post hoc analysis adjusting for study center, sedative agent before randomization, and target sedation level.

Downloaded From: http://journal.publications.chest.org/ on 08/20/2012